ATYPICAL ANTIPSYCHOTIC AGENTS

MEDICAID DRUG USE REVIEW CRITERIA FOR OUTPATIENT USE

Atypical antipsychotic medications are loosely described as those agents that are able to effectively treat psychotic symptoms without causing the extrapyramidal side effects associated with the standard antipsychotic agents. They have demonstrated superior efficacy in treating the negative symptoms of schizophrenia such as alogia, avolition, and anhedonia. The four medications available for use are clozapine, olanzapine, quetiapine, and risperidone.

Due to the benefits attributed to the atypical antipsychotic agents, they are increasingly being used as first-line therapy for the management of the manifestations of psychotic disorders. Initially, the atypical antipsychotic agents were reserved for use in patients resistant to or intolerant of traditional antipsychotic medications. The rationale for this restriction was primarily based on the relatively high acquisition cost and granulocytopenia associated with clozapine. Evidence is accruing that demonstrates improved long-term outcomes from early, effective treatment. By initiating treatment when patient's present with their first psychotic episode, total healthcare utilization may be reduced. Careful pharmacoeconomic analysis is needed to define the role of the atypical antipsychotic medications in the management of the manifestations of psychotic disorders.

1. Maximum usual dosage:

Usual and maximum adult doses are listed in Table 1. In elderly patients, atypical antipsychotics have been shown to provide relief of delirium, delusions, and other psychotic disorders of late life with fewer adverse effects than are commonly seen with standard antipsychotic medications. Dosing may be started as low as one-third to one-half the normal starting dose and titrated slowly to the desired effect so as to minimized adverse effects. Elderly patients rarely tolerate or require the doses used in healthy adults. Small clinical trials of atypical antipsychotic medication use in children with autism and various mood disorders have been conducted. Safety and efficacy in pediatric patients have not been established for any of the atypical antipsychotic medications.

2. Indication for use

Olanzapine, quetiapine, and risperidone are indicated for the management of the manifestations of psychotic disorders. Clozapine is indicated for the management of severely ill schizophrenic patients who fail to respond to standard antipsychotic drug treatment.

3. Duration of therapy

Ideal treatment duration has not been determined for the atypical antipsychotic agents. Little is known about the long-term benefits and risks of using olanzapine, quetiapine, and risperidone;

patients who are responding to an atypical antipsychotic medication should continue to be treated. Periodic reevaluation of efficacy is recommended.

4. **Duplicative therapy**

There is no evidence supporting the routine use of multiple atypical antipsychotic medications in combination. More than one atypical antipsychotic agent should be attempted as monotherapy in all patients before duplicative therapy is considered. Concomitant use with standard antipsychotic therapy, however, may be indicated during acute psychotic episodes and maintenance therapy periods. Some patients may experience breakthrough of positive symptoms or report subjective worsening of symptoms in the absence of combination therapy.

Table 1 Usual and maximum adult dose per day

Drug	**Ingredient(s)**	**Usual Dose**	**Estimated Cost Per Month (MAC)* (03/01/1999)**	**Maximum Daily Dose**
Clozapine (Clozaril)	Clozapine 25 mg and 100 mg tablets	Initiate therapy at 25 mg QD or BID then increase by 25 mg to 50 mg daily over 2 weeks to a target daily dose of 300 – 450 mg. Administer in divided doses as tolerated.	450 mg/day $370.80	Dosing should not exceed 900 mg/day.
Olanzapine (Zyprexa)	Olanzapine 5 mg, 7.5 mg, and 10 mg tablets	Initiate therapy at 5 mg or 10 mg QD. Dosage adjustments of 5 mg QD are recommended after clinical evaluation and at least one week of any previous dose change.	10 mg/day $221.77	Safety has not been assessed at doses greater than 20 mg/day.
Quetiapine (Seroquel)	Quetiapine 25 mg, 100 mg, and 200 mg tablets	Initiate therapy at 25 mg BID and increase by 25 mg to 50 mg BID on days two, tree, and four to a daily dose range of 300 mg to 400 mg. Maximum clinical effect occurred at 300 mg/day in dose-response studies.	400 mg/day $237.60	Safety has not been assessed at doses greater than 800 mg/day.
Risperidone (Risperdal)	Risperidone 1 mg, 2 mg, 3 mg, and 4 mg tablets	Initiate therapy at 1 mg BID and increase by 1 mg BID on days two and three of treatment to a target dose of 3 mg BID. Dose adjustment may then occur no sooner than one week after a previous change. Maximum efficacy has been noted at doses between 4 and 6 mg/day. Doses up to 16	6 mg/day $252.90	Safety has not been assessed at doses higher than 16 mg per day.

		mg/day have been used.		

* Prices reflect cost to Medicaid for drug only. Add $3.90 for dispensing fee per prescription.

5. Drug-drug interactions

Minor These include interactions that are poorly documented, potential harm to patient is minimal, or the incidence of the interaction is low.

Moderate These include interactions where more documentation is needed or the potential harm to the patient is less serious than the major interactions.

Major These include interactions which are well documented or may be harmful to the patient.

a. Benzodiazepine sedative-hypnotics (moderate)

Clozapine and diazepam or lorazepam may have an additive impact on cardiovascular and respiratory function leading to collapse. Concomitant administration of clonazepam or lorazepam with clozapine has been reported to cause delirium. Cases have been reported, but causality has not been determined.

b. Caffeine (minor)

Caffeine's dopaminergic activity may decrease the antipsychotic efficacy of clozapine. One case has been reported; causality has not been established.

c. Carbamazepine (moderate)

Carbamazepine may induce the metabolism of clozapine, olanzapine, quetiapine, and risperidone decreasing their efficacy. Neuroleptic malignant syndrome has been reported with concomitant use of carbamazepine and clozapine.

d. Cimetidine (moderate)

Cimetidine may inhibit the hepatic metabolism of clozapine causing an increased potential for adverse effects due to clozapine.

e. Ethanol (moderate)

Concomitant use of ethanol with quetiapine or risperidone decreases cognition and motor function.

f. Fosphenytoin - see Phenytoin

g. Lithium (minor)

Cases of diabetic ketoacidosis have been reported in patients on concomitant therapy of clozapine and lithium. Causality has not been established.

h. Macrolide antibiotics (moderate)

Clarithromycin, erythromycin, and troleandomycin may inhibit the metabolism of clozapine causing an increased potential for adverse effects due to clozapine. Azithromycin and dirithromycin should not impact clozapine metabolism significantly.

i. Phenytoin (moderate)

Fosphenytoin and phenytoin may induce the metabolism of clozapine decreasing its efficacy. Phenytoin has been shown to markedly increase the clearance of quetiapine; clinical relevance is inferred.

j. Rifamycins (moderate)

Rifabutin and rifampin may induce the metabolism of clozapine and quetiapine decreasing their efficacy

k. Risperidone (minor)

Risperidone may interfere with the metabolism of clozapine causing an increased potential for adverse effects due to clozapine.

l. Ritonavir (major)

Ritonavir may interfere with the metabolism of clozapine causing an increased potential for adverse effects due to clozapine.

m. Selective Serotonin Reuptake Inhibitors (SSRIs) (moderate)

Fluoxetine, fluvoxamine, and sertraline may interfere with the metabolism of clozapine causing an increased potential for adverse effects due to clozapine. Paroxetine does not seem to alter clozapine metabolism. Citalopram has not been reported.

One case of tardive dyskinesia has been reported with concomitant use of fluoxetine and risperidone. This reaction may be due to elevated risperidone plasma concentrations; fluoxetine may inhibit the metabolism of risperidone.

n. Thioridazine (moderate)

Thioridazine has been shown to markedly increase the clearance of quetiapine; clinical relevance is unknown.

o. Valproic Acid (moderate)

Valproic acid may increase or decrease plasma concentration of clozapine. The interaction is thought to be due to decreased clozapine protein binding. Free clozapine concentration may be normal in the presence of a low total clozapine concentration. Sedation and decreased level of functioning have been noted in patients with an elevated clozapine plasma concentration.

p. Theoretical Drug Interactions (moderate)

Cytochrome P450 IA2 inducers and inhibitors

Several enzymes are responsible for the metabolism of olanzapine. Drugs that induce or inhibit CYPIA2 may increase or decrease the elimination of olanzapine, respectively. CYPIA2 inhibition does not seem to significantly alter elimination of olanzapine; CYPIA2 induction seems to be the important interaction. Examples of CYPIA2 inducers include **phenytoin, rifampin**, and **phenobarbital**. Examples of CYPIA2 inhibitors include **erythromycin, ciprofloxacin**, and **fluvoxamine**.

Cytochrome P450 IID6 inducers and inhibitors

Drugs that inhibit the CYPIID6 isoenzyme may decrease the metabolism of risperidone and increase the incidence of adverse effects (e.g., **SSRIs, cimetidine, quinidine, and thioridazine**). CYPIID6 is a minor metabolizer of olanzapine and does not seem to significantly impact its elimination.

Cytochrome P450 IIIA4 inducers and inhibitors

Caution should be exercised when CYPIIIA4 inhibitors (e.g., **erythromycin, ketoconazole, ritonavir**) and inducers (e.g., **carbamazepine, barbiturates, rifampin**) are used concomitantly with quetiapine. Quetiapine elimination may decrease and the incidence of adverse effects associated with quetiapine may increase in the presence of CYPIIIA4 inhibitors. In the presence of phenytoin, a CYPIIIA4 inducer, quetiapine clearance is significantly increased.

Drug List Appendix

Atypical Antipsychotics
clozapine (Clozaril)
olanzapine (Zyprexa)
quetiapine (Seroquel)
risperidone (Risperdal)

Barbiturates
amobarbital (Amytal)
aprobarbital (Alurate)
butabarbital (Butisol, Sarisol)
mephobarbital (Mebaral)
methohexital (Brevital)
pentobarbital (Nembutal)
phenobarbital (Solfoton, Lumioal, Barbital)
secobarbital (Seconal)
thiopental (Pentothal)

Benzodiazepines
alprazolam (Xanax)
chlordiazepoxide (Librium, Libritabs, Mitran, Reposans-10)
clonazepam (Klonopin)
clorazepate (Tranxene, Gen-Xene)
diazepam (Valium)
estazolam (ProSom)
flurazepam (Dalmane)
halazepam (Paxipam)
lorazepam (Ativan)
oxazepam (Serax)
prazepam (Centrax)
quazepam (Doral)
temazepam (Restoril)
triazolam (Halcion)

Macrolide antibiotics
azithromycin (Zithromax)
clarithromycin (Biaxin)
dirithromycin (Dynabac)
erythromycin (E-Mycin, Ery-Tab, E-base, Eryc, PCE Dispertab, Ilosone, E.E.S. 400, EryPed, Erythrocin)
troleandomycin (Tao)

Rifamycins
rifabutin (Mycobutin)
rifampin (Rifadin, Rimactane)

Selective Serotonin Reuptake Inhibitors (SSRIs)
citalopram (Celexa)
fluoxetine (Prozac)
fluvoxamine (Luvox)
paroxetine (Paxil)
sertraline (Zoloft)

References

1. Clozaril [product information]. East Hanover, NJ: Novartis Pharmaceuticals; 1997.

2. Crismon ML, Dorson PG. Schizophrenia. In: Dipiro JR, Talbert RL, Yee GC, et al., eds. Stamford, CT: Appleton & Lange 1997;1367-94.

3. Collaborative working group on clinical trial evaluations. Treatment of special populations with the atypical antipsychotics. J Clin Psychiatry 1998;59(suppl 12):46-52.

4. Daniel DG, Whitcomb SR. Treatment of the refractory schizophrenic patient. J Clin Psychiatry 1998;59(suppl 1):13-19.

5. Hansten PD, Horn JR, eds. Drug Interactions Analysis and Management. Vancouver, WA: Applied Therapeutics, Inc.; 1997.

6. Lieberman JA. Atypical antipsychotic drugs as a first-line treatment of schizophrenia: a rationale and hypothesis. J Clin Psychiatry 1996;57(suppl 11):68-71.

7. Olin BR, ed. Facts and comparisons. St. Louis: Wolters Kluwer Company; 1996.

8. Risperdal [product information]. Titusville, NJ: Janssen Pharmaceutical, Inc.; 1996.

9. Seroquel [product information]. Wilmington, DE: Zeneca Pharmaceuticals; 1997.

10. Tatro DS, ed. Drug Interaction Facts. St. Louis, MO: Facts and Comparisons; 1997.

11. Zyprexa [product information]. Indianapolis, IN: Eli Lilly Industries, Inc.; 1996.

Clozapine (Clozaril®)

	CRITERIA	RATIONALE
Maximum dose per day	**900 mg/day**	**Potential for seizures is dose related.**
Indication for use	**Management of severely ill schizophrenic patients who fail to respond to standard antipsychotic drug therapy.**	**Indications supported by product labeling and clinical practice.**
Duration of therapy	**Based on the individual patient's response to treatment**	**Responding patients should continue treatment.**
Duplicity of therapy	Concurrent standard antipsychotic medications	Combination therapy may be indicated upon failure of a reasonable trial of monotherapy with a standard and atypical antipsychotic agent.
Drug-drug interaction	Benzodiazepines	Potential cardiorespiratory toxicity
	Caffeine	Decreased efficacy
	Lithium	May promote development of ketoacidosis
	Cimetidine	Inhibit hepatic metabolism of clozapine
	Macrolide antibiotics	
	Risperidone	
	Ritonavir	
	Serotonin reuptake inhibitors	
	Carbamazepine	Induce hepatic metabolism of clozapine
	Phenytoin	
	Rifamycins	
	Valproic acid	Decreases total clozapine plasma concentrations
Drug-disease interaction	Myeloproliferative disorders	Clozapine can cause granulocytopenia.
	History of clozapine-induced agranulocytosis or severe granulocytopenia	
	Uncontrolled epilepsy	Clozapine may induce or exacerbate seizure disorder.

	Prostatic enlargement	The anticholinergic effect of clozapine may worsen these medical problems.
	Narrow angle glaucoma	
	Severe CNS depression	The CNS effects of clozapine may worsen these medical problems
	Coma	

Olanzapine (Zyprexa^{Ò})

	CRITERIA	RATIONALE
Maximum dose per day	**20 mg/day**	**Safety has not been assessed at higher doses.**
Indication for use	management of the manifestations of psychotic disorders	Indications supported by product labeling and clinical practice.
Duration of therapy	Based on individual patient response to treatment.	Responding patients should continue treatment.
Duplicity of therapy	Concurrent standard antipsychotic medications	Combination therapy may be indicated upon failure of a reasonable trial of monotherapy with a standard and atypical antipsychotic agent.
Drug-drug interaction	Carbamazepine	Increases the metabolism of olanzapine by approximately 50%
Drug-disease interaction	Disease states that decrease seizure threshold	Olanzapine may cause seizures.
	History of seizure disorder	
	Hyperprolactinemia	Olanzapine elevates prolactin levels.

Quetiapine (Seroquel^{Ò})

	CRITERIA	RATIONALE
Maximum dose per day	800 mg/day	Safety has not been assessed at higher doses
Indication for use	Management of the manifestations of psychotic disorders	Indications supported by product labeling and clinical practice.
Duration of therapy	Based on individual patient response to treatment.	Responding patients should continue treatment.
Duplicity of therapy	Concurrent standard antipsychotic medications	Combination therapy may be indicated upon failure of a reasonable trial of monotherapy with a standard and atypical antipsychotic agent.
Drug-drug interaction	Ethanol	Concomitant use decreases cognition and motor function
	Phenytoin	Increases hepatic metabolism of quetiapine
	Thioridazine	Increases clearance of quetiapine
Drug-disease interaction	Studies have not identified specific drug-disease interactions.	

Risperidone (Risperdal^{Ò})

	CRITERIA	**RATIONALE**
Maximum dose per day	16 mg/day	Safety has not been assessed at higher doses
Indication for use	management of the manifestations of psychotic disorders	Indications supported by product labeling and clinical practice
Duration of therapy	Based on individual patient response to treatment.	Responding patients should continue treatment.
Duplicity of therapy	Concurrent standard antipsychotic medications	Combination therapy may be indicated upon failure of a reasonable trial of monotherapy with a standard and atypical antipsychotic agent.
Drug-drug interaction	Carbamazepine	Increased hepatic metabolism of risperidone
	Clozapine	Risperidone inhibits the hepatic metabolism of clozapine.
	Ethanol	Impaired cognitive and motor performance
	Fluoxetine	Tardive dyskinesia was reported during concomitant use of fluoxetine and risperidone. Monitor closely.
Drug-disease interaction	Hyperprolactinemia	Risperidone elevates prolactin serum concentration.
	History of seizure disorder	Risperidone may cause seizures.
	Cardiac diseases	Risperidone may cause QTc interval prolongation. Monitor closely.